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TITLE: Development of Pain Endpoint Models for Use in Prostate Cancer Clinical Trials and Drug Approval

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14. ABSTRACT

OBJECTIVE: The objective of this work is to establish standard methods for measuring pain palliation and pain progression in prostate cancer clinical trials that are feasible, methodologically rigorous, and meet regulatory requirements for drug approval and labeling. The primary aim of this award is to conduct an observational longitudinal study in men with castrate-resistant metastatic prostate cancer receiving docetaxel-based chemotherapy, in order to establish key design elements of a pain endpoint model which can be used in pivotal trials. SUMMARY: At the close of the third year, we report the following progress: (1) we anticipate the study designed to address Aim 1 to open at UNC in November/December 2013, and the study will open at the additional sites in Q1 2014; (2) a manuscript resulting from the work described in Aim 2 has been written and approved by all authors and by the industry sponsor. This manuscript is planned for submission to a peer reviewed journal during the next quarter; and (3) the manuscript resulting from work described in Aim 3 was accepted for publication by the journal "Cancer" and it is currently in the press. The title of the manuscript is: "Pain Palliation Measurement in Cancer Clinical Trials: The US Food and Drug Administration Perspective".

15. SUBJECT TERMS
None provided.

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TABLE OF CONTENTS

INTRODUCTION 4
BODY 4
KEY RESEARCH ACCOMPLISMENTS 6
REPORTABLE OUTCOMES 7
CONCLUSIONS 8
REFERENCES 8
APPENDICES 8

INTRODUCTION

Pain is common in men with metastatic prostate cancer and can substantially impair functioning and quality of life. Regulatory standards for the design of symptom endpoints have evolved substantially over the past decade (culminating in an FDA Guidance document issued on this topic in December 2009), and approaches used previously to assess cancer-related pain and analgesic use are no longer considered sufficiently methodologically rigorous. The objective of this work is to establish standard methods for measuring pain palliation and pain progression in prostate cancer clinical trials that are feasible, methodologically rigorous, and meet regulatory requirements for drug approval and labeling. The primary aim of this award is to conduct an observational longitudinal study in men with castrate-resistant metastatic prostate cancer receiving docetaxel-based chemotherapy, in order to establish key design elements of a pain endpoint model which can be used in pivotal trials. The second aim is to analyze data from a feasibility study of pain assessment nested within an industry-sponsored phase II treatment trial conducted in the Prostate Cancer Clinical Trials Consortium. The third aim is to conduct literature reviews and moderate a consensus meeting, with input from investigators in the Prostate Cancer Clinical Trials Consortium, FDA Office of Oncology Drug Products, FDA Study Endpoint and Label Development Team, and FDA Division of Anesthesia, Analgesia and Rheumatology Products, in order to establish discrete guidelines and produce a publication delineating key methodological components of pain studies in prostate cancer.

BODY

In this section, we report the progress made towards the completion of each Aim.

Aim 1 To conduct an observational longitudinal study in men with castrate-resistant metastatic prostate cancer receiving docetaxel-based chemotherapy, in order to establish key design elements of a pain endpoint model which can be used in pivotal trials.

University of North Carolina at Chapel Hill is now the coordinating center for the study data and contracts. Administrative logistical delays related to institutional move have led to substantial delays in opening the study. The PI has been working closely with grant offices at Memorial Sloan Kettering Cancer Center, University of North Carolina as well as the Department of Defense to move this process forward expeditiously. Currently enrollment is awaiting approval of award transfer from Department of Defense.

The table below lists the first three Tasks of Aim 1 as outlined in the Statement of Work (PC100563 Basch 7-20-2011, revised 4-20-2013) and the current status is noted:

Table 1. Current Status of Tasks Outline in Scope of Work

Task 1. Develop study protocol and obtain IRB approval (Months 1 – 6) **IN PROGRESS**
1a. Submit Letter of Intent to Prostate Cancer Clinical Trials Consortium (Month 3) **Completed**
1b. Elicit input on study design from collaborators (Months 1 – 2) **Completed**
1c. Draft study protocol, including all case report forms (CRFs) (Months 1 – 3) **Completed**
1d. Submit protocol to departmental review committees at MSKCC (Month 3) **Completed**
1e. Obtain IRB approval at MSKCC (Months 14 – 16) **Completed – 6/5/2012**
1f. Submit for HRPO review (Month 19-21) **Completed – 9/17/2012**
New: Revise protocol to indicate UNC is now coordinating center. Submit for IRB approval at UNC (Month 20) **Completed – 01/29/2013**
New: Submit UNC protocol and site documents for HRPO approval **Completed – 08/15/2013**
1g. Submit for IRB review at participating sites (Johns Hopkins, Oregon Health & Sciences University, University of Washington) (Month 8) Johns Hopkins **Approved 5/09/2013** Oregon Health &Sciences University **Submitted – 5/10/2013** University of Washington **In progress (requires sub-contract)**
New: Submit Johns Hopkins, Oregon Health & Sciences University, and University of Washington protocol and site documents for HRPO approval Johns Hopkins **Approved 8/29/2013** Oregon Health &Sciences University **Approved 08/27/2013** University of Washington – **awaiting IRB approval**
Task 2. Prepare for data collection and analysis (Months 1 – 6) **IN PROGRESS**
2a. Develop IVRS platform (Months 1 – 3) **Completed**
2b. Develop study databases on secure, password-protected server (Months 3 – 6) **Completed**
2c. Draft statistical analysis plan and elicit feedback from collaborators (Months 1 – 6) **In Progress**
Task 3. Implement study protocol (Months 21-45) **IN PROGRESS**
3a. Conduct site orientations (Month 21) **Slide deck for site orientations is complete.**
3b. Recruit and enroll patients (Months 21-32) **We anticipate patient enrollment to begin Nov./Dec. 2013 at UNC.**

3c. Track accrual/follow-up, conduct weekly telephone meetings with site data managers, and conduct monthly telephone meetings with site PIs (Months 21-45)
Task 4. Analyze study data (Months 21 – 48) 4a. Import data from IVRS to secure study database (Months 21 – 45) 4b. Collect CRFs completed by clinic staff on monthly basis (Months 21 – 45) 4c. Enter CRF data into secure study database (Months 21 – 45) 4d. Perform data quality audits on monthly basis (Months 21 – 45) 4e. Analyze data, per SAP, and prepare tables and figures (Months 45 – 48) 4f. Prepare manuscripts and abstracts with input from collaborators (Months 45 – 48)

We are considering increasing enrollment at each of the four sites because in contract negotiation with MSKCC Dept of Medicine the amount of support requested for patient enrollment was well beyond what we had anticipated providing from other funding sources. The award includes funding for patient enrollment at four sites (UNC, Johns Hopkins, OHSU, and University of Washington). The patient survey and study databases have been built on the MSKCC Webcore system, and this effort is paid for through the award.

Aim 2 To analyze data from a feasibility study of pain assessment nested within an industry-sponsored phase II treatment trial conducted in the Prostate Cancer Clinical Trials Consortium.

Data analysis from pain assessment nested in a phase II clinical trial of cabozantinib has been analyzed. A manuscript has been written and approved by all co-authors and by industry sponsor. This manuscript is planned for submission to a peer reviewed journal during next quarter.

Aim 3 To conduct literature reviews and moderate a consensus meeting, with input from investigators in the Prostate Cancer Clinical Trials Consortium, FDA Office of Oncology Drug Products, FDA Study Endpoint and Label Development Team, and FDA Division of Anesthesia, Analgesia and Rheumatology Products, in order to establish discrete guidelines and produce a publication delineating key methodological components of pain studies in prostate cancer.

A meeting with the relevant stakeholders was held. A manuscript was written with FDA collaboration. This manuscript was accepted by the journal “Cancer” and it is currently in press.

Reference:

Basch E, Trentacosti AM, Burke LB, Kwitkowski V, Kane RC, Autio KA, Papadopoulos E, STansbury JP, Kluetz PG, Smith H, Justice R, Pazdur R. Pain Palliation

Measurement in Cancer Clinical Trials: The US Food and Drug Administration Perspective. Cancer 2013; in press.

KEY RESEARCH ACCOMPLISMENTS

Aim 1. The protocol and appendices are completed. The coordinating center was transitioned from MSKCC to UNC. The revised protocol, indicating UNC as the coordinating center, has been approved by UNC IRB and HRPO. IRB approval has been obtained at Oregon Health &Sciences University and Johns Hopkins. University of Washington is in progress of obtaining IRB approval. The documents for OHSU and Johns Hopkins have been submitted to HRPO. The study data collection interface was completed and user tested. The automated telephone system for patient reporting of symptoms and analgesic use was completed and user tested.

Milestone 1. Completed study protocol, UNC IRB approval

Aim 2. A study was designed and conducted with an industry sponsor phase II trial. Results were analyzed and manuscript was completed by all authors and company. Journal submission is planned in the near future.

Aim 3. The following manuscript has been prepared as a result of a series of meetings with FDA and is currently under review at Journal of Clinical Oncology: "Pain palliation measurement in cancer clinical trials: the FDA perspective". This work addresses:

Milestone 2. Manuscript delineating guidelines and key methodological component of pain studies in prostate cancer. Lead author: Basch (Month 21)

REPORTABLE OUTCOMES

Aim 1 – Research is in progress

Aim 2 – Research findings include:

1. Collection of pain data via automated telephone system is feasible in a clinical trial including symptomatic men with advanced metastatic CRPC that is heavily pretreated.
2. Tabulation of total analgesic dose is feasible and can be combined with pain intensity data in clinical trial response and definition.
3. Content validity of a patient pain diary was established
4. Patient understanding and acceptance of the worst pain NRS was established in this population (Bennett et al, ASCO and ISPOR, 2013)
5. Related end points including sleep quality and general activity were significantly associated with pain response.

Results from this phase II pain assessment served as rationale for design of phase III trial with primary pain endpoints.

Aim 3 – A manuscript is in press (Basch et al). Key findings of this paper include articulations of current FDA thinking about the design end points in cancer trails. This includes:

1. Methodological criteria for selective pain measurements
2. Approaches for analgesic tabulation
3. Approach to demonstrating durability of pain response
4. Role of pain end points in drug approval and labeling
5. Issues related to pain measurements in open and unblinded trials

CONCLUSIONS

Substantial progress has been made in Aim 2 and 3 of this project with one manuscript in press and a second manuscript ready for journal submission. The progress of Aim 1 has been substantially delayed due to administrative and logistical challenges related to the award transfer from MSKCC to UNC. Close communication with Department of Defense about this process has facilitated a clear plan moving forward to accomplish this aim on a revised schedule.

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Basch E, Trentacosti AM, Burke LB, Kwitkowski V, Kane RC, Autio KA, Papadopoulos E, STansbury JP, Kluetz PG, Smith H, Justice R, Pazdur R. Pain Palliation Measurement in Cancer Clinical Trials: The US Food and Drug Administration Perspective. Cancer 2013; in press.

Bennett AV, Atkinson TM, Heon N, O'Keefe B, Scheffold C, Schimoller F, Basch E. Qualitative assessment of the Brief Pain Inventory (BPI) "pain at its worst in the last 24 hours" item to support assessment of pain as a clinical trial endpoint in metastatic castrate resistant prostate cancer (mCRPC) per FDA labeling standards. Abstract. American Society of Clinical Oncology. Chicago IL, June 1-5, 2013.

Bennett AV, Eremenco S, Heon N, Scheffold C, Schimmoller F, Weitzman AL, Basch E. Mode equivalence of Interactive Voice Response (IVR) and paper versions of the Brief Pain Inventory (BPI) "worst pain" item in metastatic resistant prostate cancer (MCPRC) evaluated conceptually using qualitative methods. International Society for Pharmacoeconomics and Outcomes Research. 16th Annual European Congress, Dublin, Ireland, November 2-6, 2013.

APPENDICES

None